

# **SARS-CoV-2 mRNA Vaccination and Graves' Disease: a report of 12 cases and review of the literature**

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## Abstract

### Context and objective:

Thyroid autoimmunity has been reported to be associated with SARS-CoV-2 and the SARS-CoV-2 vaccination recently. We report a series of patients who presented with new onset or relapse of Graves' disease related hyperthyroidism shortly after receiving the SARS-CoV-2 mRNA vaccine at a single tertiary institution in Singapore.

### Methods and results:

We describe 12 patients who developed hyperthyroidism within a relatively short interval (median onset of 17 (range: 5 - 63) days) after receiving the SARS-CoV-2 mRNA vaccine. The majority were females (11/12) with median age of 35.5 (range: 22-74) years. Six patients had new onset hyperthyroidism, while the other six had relapse of previously well-controlled Graves' disease. TSH Receptor antibody concentrations ranged from 2.4-32 IU/L. Majority of the patients were able to go for the second dose of the vaccine without any further exacerbations. Literature review revealed 21 other similar cases reported from across the world.

### Conclusion:

Our case series provide insight into the characteristics of individuals in whom Graves' disease was triggered by the SARS-CoV-2 vaccination. Clinicians need to be vigilant of precipitation or exacerbation of autoimmune thyroid disorders in predisposed individuals after exposure to the SARS-CoV-2 vaccination. Further epidemiological and mechanistic

studies are required to elucidate the possible associations between the SARS-CoV-2 vaccines and the development of thyroid autoimmunity.

**Keywords:** SARS-CoV-2 vaccine, Graves' disease, hyperthyroidism

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## Introduction:

The SARS-CoV-2 virus pandemic has affected more than 275 million people worldwide (1). Globally, vaccination efforts are being ramped up to reduce mortality and transmission of the virus. To date, there are nine vaccines approved by the World Health Organization (2), which can be classified broadly based on the types of viral components (whole virus versus individual viral component) used in the production (3). The RNA-based vaccines (Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273) are two widely administered vaccines.

The global prevalence of hyperthyroidism ranges from 0.1% to 2.5% in iodine sufficient countries, of which approximately 70-80% are Graves' disease. In iodine deficient regions, the prevalence of hyperthyroidism ranges from 0.4 – 2.9%. Graves' disease accounts for 50% of these cases (4). New onset or relapse of Graves' disease is reported to occur within days (up to 38 days) after receiving the first or second dose of SARS-CoV-2 vaccines, predominantly the RNA-based ones (5-17).

Singapore is an iodine sufficient, island city-state in maritime Southeast Asia. The population of Singapore comprises of approximately 5.4 million people in three ethnic groups - Chinese, Malays and Indians (18). The country's vaccination drive against COVID-19 started in January 2021 and more than 90% of the eligible population have completed the full regimen (19). Majority of the population received the RNA-based vaccines.

We describe a case series of 12 patients with new onset or relapsed Graves' disease related hyperthyroidism post vaccination, presenting to a single tertiary Endocrinology clinic in Singapore.

### **Case Series Description:**

We included all consecutive patients who presented with new onset or exacerbation of hyperthyroidism to our center with a temporal sequence to the vaccine between January to December 2021. All the participants signed an informed consent. The study was approved by our institutional review board (DSRB Ref: 2021/00960).

Twelve patients presented with Graves' hyperthyroidism after they received the SARS-CoV-2 mRNA vaccines. Six patients had new onset symptoms, while the other six had relapse of previously well-controlled condition. None of the patients were known to have previous SARS-CoV-2 infection. The patients' characteristics, laboratory results and progress are summarized in Table 1. There were 11 females: 9 Chinese and 3 non-Chinese (1 Malay and 2 Filipinos). One patient was a smoker. Five patients had a family history of thyroid disorders. Their median age was 35.5 (range: 22-74 years). All patients had a palpable non-tender diffuse goiter and 3 patients had signs and symptoms suggestive of mild to moderate thyroid eye disease. The overall median time to onset of hyperthyroid symptoms was 17 (IQR 8 – 27) days. Five patients developed clinical and/or biochemical hyperthyroidism after receiving the first dose of the SARS-CoV-2 mRNA vaccine with a median onset of 7 (IQR 5 – 21) days. The other 7 patients developed hyperthyroidism only after the second dose of the SARS-CoV-2 vaccine, with a median time of symptom onset of 21 (IQR 11 – 31) days after

the second dose. At initial diagnosis, the median free thyroxine (FT4) concentration [Chemiluminescent immunoassay; Beckman Coulter Dxl-800] was 49.5 pmol/L (IQR 24.5 – 69) (RI: 8-16). Free triiodothyronine (FT3) [Chemiluminescent immunoassay; Beckman Coulter Dxl-800] was performed in 4/12 with concentrations ranging from 6.3 pmol/L to more than 40 pmol/L (RI: 3.5 – 6.0). Thyroid stimulating hormone (TSH) [Chemiluminescent immunoassay; Beckman Coulter Dxl-800] was suppressed to <0.01 mIU/L in 6/12 and was close to 0.01 mIU/L in others. The median thyroid stimulating hormone receptor antibody (TRAb) [Eurommune Anti-TSHReceptor (TRAb) Fast ELISA, RRID:SCR\_021945] concentration was 6.2 IU/L (Range 2.4-32) (RI: < 1) at diagnosis. For majority of the patients who relapsed, there was a clear increase in free T4 and suppression of TSH shortly after receiving the vaccine

The five patients (Patients 1, 2, 4, 7 and 12) who developed hyperthyroidism after the first dose were treated with carbimazole as per usual clinical practice in our institution. Patients 1, 2, 4 and 12 did not experience exacerbation of hyperthyroidism clinically and biochemically after the second dose (Table 1). No adjustments to the anti-thyroid medication or beta-blockade doses were required after the second dose. Patient 7 already developed hyperthyroid symptoms 21 days after receiving the first dose of vaccine but proceeded with the second dose before finally presenting to his primary endocrinologist. Nine patients achieved normal FT4 within a median time of 42 (IQR 31 – 58) days.

## Literature Review:

A literature review was performed in PubMed, google scholar using keywords thyroid, hyperthyroidism, Graves' disease, thyroiditis, COVID-19, or SARS-CoV-2 vaccination. We found 21 other cases of Graves' disease (5-17) (Table 2) occurring shortly after the SARS-CoV-2 vaccination.

Similar to our case series and background epidemiology of Graves' disease (20), 13/21 cases were females in all age groups. Majority of cases presented after mRNA vaccines (12/21), while the other 9 cases presented after receiving vector-based vaccines. Sixteen developed new onset hyperthyroidism, while 3 developed worsening of known Graves' hyperthyroidism. There was one interesting presentation of a patient who converted to hypothyroidism from hyperthyroidism after vaccination (6) and another individual had newly diagnosed Graves' disease with concurrent subacute thyroiditis (14). Among these cases, 9 developed symptoms after the first dose, 7 after the second dose, 4 after a dose (first or second dose was not specified) and 1 after receiving a vector-based booster dose (this patient had received inactivated whole virus vaccine 3 months prior). There was paucity of follow-up clinical and biochemical data for majority of the patients, and there was insufficient information on whether those who developed new-onset or relapsed Graves' disease were able to tolerate the second vaccine dose. The follow-up progress was described in only one patient, who was diagnosed with new onset Graves' disease shortly after the first mRNA vaccine dose and received the second dose of vaccine 71 days later with a documented thyroid function test showing no further exacerbation (11).

Apart from Graves' disease, subacute thyroiditis is a differential diagnosis to consider in thyrotoxic individuals. It is important to distinguish both entities as the management and course of disease is different. Based on recent reports of subacute thyroiditis cases occurring after receiving the SARS-CoV-2 vaccine (10, 13-14, 21-37), majority of these patients became symptomatic within short days to weeks with neck pain being the chief complaint. The TRAb concentrations were normal in all patients upon presentation, while the erythrocyte sedimentation rate was elevated in all cases. The diagnosis of subacute thyroiditis was supported by thyroid scintigraphy findings of reduced tracer uptake. Majority of these patients responded well to a combination of non-steroidal anti-inflammatory drug, glucocorticoid and beta-blocker with full resolution of symptoms and normalization of thyroid function shortly after initiation of treatment.

#### **Discussion:**

The RNA-based SARS-CoV-2 vaccines have been extensively administered since its approval. We report an extensive case series with temporal sequence of new-onset or relapse of Graves' disease potentially triggered by exposure to the SARS-CoV-2 mRNA vaccines. In our case series, we observed that the exacerbation of hyperthyroidism can occur after the first or subsequent doses of the vaccine. Importantly, all the patients were able to tolerate a subsequent booster dose of SARS-CoV-2 mRNA vaccine without further exacerbation of hyperthyroidism.

Whether thyroid autoimmunity may develop among individuals exposed to other types of SARS-CoV-2 vaccines (e.g. DNA-based) is currently unclear. In the literature, only a handful

of similar precipitation of Graves' disease and subacute thyroiditis has been reported after influenza or H1N1 vaccination (38 – 41). These cases may be under reported as clinicians may not associate the condition with the vaccination.

While in the above cases, the temporal sequence suggests that thyrotoxicosis may be related to the SARS-CoV-2 vaccination, there is currently no evidence to prove a causal relationship. The relationship can only be postulated to be at best as "probable". The vaccination may serve as a precipitating agent. Using the analogy recently published in JCEM (42), the vaccination may at best be considered to be another rain cloud in the trajectory of Graves' disease. In an individual with pre-existing Graves' disease it may serve as a role of a sudden rain cloud which may disrupt the steady state and will need re-enforcement of an umbrella; while in a new onset Graves' disease it may be a sudden rain cloud which disrupts the baseline latency of the autoimmune problem and precipitates a full blown disease (42). However, baseline predisposing factors would have been present in the individuals and the vaccine cannot be considered as a causative agent. Selenium supplementation and optimizing Vitamin D levels may be considered to minimize aberrant autoimmune reactions in patients known to have pre-existing autoimmune disorders (43).

There is a concern about the possible deleterious effect of the 2<sup>nd</sup> dose in patients who present after the first dose or booster doses. This limited series shows that – for Graves' hyperthyroidism, they can go for a second dose without any significant problems if treatment is initiated before the vaccination and hyperthyroidism is controlled. These patients can be treated like we prepare patients for surgery and efforts need to be made to control free T4 and free T3 concentrations before the subsequent dose as much as possible.

Possible mechanisms by which these vaccines result in exacerbation of thyroid autoimmunity includes : 1. Direct activation of the ACE2 receptors on the thyroid gland (44); 2. Molecular mimicry with cross reactivity with components of the SARS-CoV-2 mRNA vaccines encoding proteins that may cross-react with thyroid antigens (45); 3. When the SARS-CoV-2 mRNA vaccine carrying specific proteins that mimic thyroid antigens are presented to the antigen-presenting cells, the T and B lymphocytes become activated and trigger downstream immune signaling pathways (46), which could trigger Graves' disease in predisposed individuals; 4. the induction of autoimmunity by vaccine adjuvants, resulting in the autoimmune/inflammatory syndrome (ASIA).

The differential activation of T and B lymphocytes plays a crucial role in the pathogenesis of Graves' disease. Previously, Graves' disease was thought to be predominantly driven by humoral cellular responses mediated by T-helper 2 (Th2) cells (47). However, recent evidence suggests that cell-mediated responses involving T-helper 1 (Th1) cells, characterized by interferon-gamma (IFN- $\gamma$ ), occur in the early phase of Graves' disease. The T-cell repertoire then progressively shifts towards Th2 in the later course of the disease (48, 49). Cytokines, including IFN- $\gamma$  and tumour necrosis factor-alpha, have synergistic effects in promoting the synthesis of Th1 associated chemokines, which may, in turn, perpetuate thyroidal inflammation (48). The robust Th1 cellular response, characterized by high IFN- $\gamma$  levels, induced by the SARS-CoV-2 mRNA vaccine (50, 51) could be one of the possible mechanisms underpinning the unmasking of Graves' disease in predisposed individuals or trigger relapse in a previously well-controlled individual with Graves' disease.

Another possible mechanism mediating the development of Graves' disease could be associated with the induction of autoimmunity by vaccine adjuvants, resulting in the autoimmune/inflammatory syndrome (ASIA). This syndrome has been reported with exposure to other vaccines, including influenza, hepatitis, and human papillomavirus, as well as vaccine adjuvants such as mineral oils and polyethylene glycol (PEG) (8). The RNA-based vaccines carrying modified viral proteins are delivered to the host cells via lipid nanoparticles adjuvants to increase the immunogenicity of the vaccine (52). As one of the lipid adjuvants is PEG, the exposure could potentially induce an exaggerated immune response and precipitate the development of thyroid autoimmunity (53). Despite attempts to describe the underlying mechanisms, ASIA remains poorly understood. Enhanced vigilance to identify more potential cases of ASIA, coupled with detailed evaluation of each case is crucial to further characterize this entity.

## **Conclusion**

Our case series provide insight into the characteristics of individuals in whom Graves' disease was triggered by SARS-CoV-2 vaccination. Most of the patients were able to go for a subsequent dose without any further exacerbations. With the rapid emergence of new SARS-CoV-2 variants, the need for regular booster vaccinations may become a possibility in the near future. We believe that the SARS-CoV-2 vaccinations or boosters should not be delayed given the clear protection against severe disease conferred by the vaccine. Increased awareness among endocrinologists and primary care physicians and patients is required for early identification of a relapse or new onset Graves' disease. With timely diagnosis and prompt initiation of treatment, further doses of the SARS-CoV-2 vaccine can be safely administered and minimizes unnecessary delay in completing the vaccination schedule. Further epidemiological and mechanistic studies are required to elucidate the

possible associations between the SARS-CoV-2 vaccines and the development of thyroid autoimmunity.

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**Author contributions:** CYJ, RD, conceptualized the study, recruited the participants, performed data analysis, data interpretation, literature review, wrote the manuscript and critically reviewed manuscript. AT, LHL conceptualized the study, recruited the participants, and critically reviewed the manuscript. All other authors contributed towards recruitment and critically reviewed the final manuscript.

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**Table 1:** Demographic, clinical and laboratory characteristics of our cohort of patients with Graves' disease after exposure to SARS-CoV-2 mRNA vaccine

Pat ien t	Age /Sex/ Eth nicity	F H x	Sm oki ng	Go itre	T E D	Ne w ons et vs GD rel aps e	Time of sympt om onset after vaccin ation	TFT at diag nosi s/ rela pse	FT3 at diag nosi s/ rela pse	TRA b at diag nosi s/ rela pse	Exace rbatio n of sympt oms after secon d dose (if GD diag nos ed/ relaps ed 1 <sup>st</sup> dose)	TFT pre 2 <sup>nd</sup> dose (if GD diag nose d/ relap sed after 1 <sup>st</sup> dose)	TFT post 2 <sup>nd</sup> dose (if GD diag nos ed / relap sed after 1 <sup>st</sup> dose)	Treat ment given	Tim e to nor mal FT4 (day s)	Ti me to nor mal FT 3 (da ys)
1	33/F Chinese	Y	No	Yes	No	No	7 days after 1 <sup>st</sup> dose	FT4 45 TSH 0.01	Not don e	7.3	No	Not done	FT4 14 TSH 0.01 (don e 4 days after 2 <sup>nd</sup> dose) *no chan ge in carbi mazo le and propr anolo l dose	Carbi mazo le 30mg OM and propr anolo l 20mg BD	28	NA
2	37/F Filipino	N	No	Yes	No	No	7 days after 1 <sup>st</sup> dose	FT4 60 TSH < 0.01	Not don e	3.8	No	FT4 38 TSH < 0.01	FT4 8 TSH 0.32 (don e 3 week s after 2 <sup>nd</sup> dose) *no	Carbi mazo le 20mg OM Propr anolo l 10mg BD	32	NA

													change in carbimazole and propranolol dose			
3	37/F Filipino	N	No	Yes	Yes	Never	21 days after 2 <sup>nd</sup> dose	FT4 72 TSH < 0.01	Not done	11.2	NA	NA	NA	Carbimazole 20mg OM Propranolol 10mg BD	53	NA
4	34/F Malay	Y	No	Yes	Yes	Never	26 days after 1 <sup>st</sup> dose	FT4 68 TSH 0.01	23.8	32	No	Not done	FT4 7 TSH 0.01 done 1 month after 2 <sup>nd</sup> dose *no change in carbimazole and propranolol dose	Carbimazole 30mg OM Propranolol 10mg TDS	58	58
5	33/F Chinese	N	No	Yes	No	Never	9 days after 2 <sup>nd</sup> dose	FT4 29 TSH < 0.01	Not done	4.6	NA	NA	NA	Carbimazole 30mg OM Propranolol PRN	64	NA
6	43/F Chinese	N	No	Yes	No	Never	13 days after 2 <sup>nd</sup> dose	FT4 70 TSH < 0.01	> 40	6.2	NA	NA	NA	Carbimazole 20mg OM Beta-blockade not required	29	57
7	59/ M Chinese	Y	No	Yes	Yes	Relapsing	21 days after	FT4 49 TSH	Not done	12.8	No	Not done	FT4 49 TSH <	Carbimazole	Still elevated	NA

	ese							1 <sup>st</sup> dose (delayed seeking medical attention till after 2 <sup>nd</sup> dose)	< 0.01					0.01 (first TFT done only after 2 <sup>nd</sup> dose despite baseline to symp tom onset prior)	dose incre ased from 7.5m g daily (at base line) to 15mg daily Beta- block ade not requi red		
<b>8</b>	74/F Chinese	Y es	No	Yes	No	Relative	Asymp tomati c (TFT perfor med as part of routin e follow -up 11 days after 2 <sup>nd</sup> dose	FT4 14 TSH 0.02	Not done	6.2	NA	NA	NA	Carbi mazo le 2.5m g daily Beta- block ade not requi red	NA (FT4 nor mal at diag nosi s)	NA	
<b>9</b>	25/F Chinese	Y es	No	Yes	No	Relative	Asymp tomati c (TFT perfor med as part of routin e follow -up 31 days after 2 <sup>nd</sup> dose	FT4 15 TSH 0.01	6.3	2.9	NA	FT4 14 TSH 1.41	FT4 15 TSH 0.01	Carbi mazo le 5mg daily Beta- block ade not requi red	NA (FT4 nor mal at diag nosi s)	12 3	
<b>10</b>	41/F Chinese	No	No	Yes	No	Relative	28 days from 2 <sup>nd</sup> dose	FT4 50 TSH < 0.01	Not done	3.9	NA	Not done	Not done	Carbi mazo le 20mg daily Beta- block ade not requi red	31	NA	
<b>11</b>	24/F Chinese	No	Yes (ex- sm oke	Yes	No	Relative	Asymp tomati c (TFT done	FT4 20 TSH 0.01	Not done	2.4	NA	NA	NA	Carbi mazo le incre	42	NA	



Table 2: Summary of demographic, clinical and laboratory characteristics of the existing 21 cases of Graves' disease post SARS-CoV-2 vaccination in the literature

Reference	Sex/Age (years)	Country	Vaccine	Co-morbidities	New vs. relapse of GD	Days of symptom onset
5	Male, 52	Italy	mRNA	Diabetes mellitus, vitiligo	New	28 days after 2 <sup>nd</sup> dose
6	Female, 40	Hong Kong	mRNA	Hypothyroidism	Switch to hyperthyroidism	38 days after 2 <sup>nd</sup> dose
7	Male, 70	Thailand	Viral vector	Not reported	New	2 days after 2 <sup>nd</sup> dose
8	Female, 40	Mexico	mRNA	past COVID infection	New	2 days after receiving a dose
8	Female, 28	Mexico	mRNA	None	New	3 days after receiving a dose
9	Male, 46	Austria	mRNA	None	New	15 days from 1 <sup>st</sup> dose
10	Female, 38	Spain	mRNA	Schizophrenia	New	12 days from 1 <sup>st</sup> dose
11	Female, 64	Japan	mRNA	Colorectal cancer, diabetes mellitus, obesity	New	4 days from 1 <sup>st</sup> dose
12	Female, 38	USA	mRNA	Not reported	New	5 days after 1 <sup>st</sup> dose
12	Female, 63	USA	mRNA	Not reported	New	7 days after 1 <sup>st</sup> dose
12	Male, 30	USA	mRNA	Not reported	New	28 days after

						2 <sup>nd</sup> dose
13	Female, 35	Australia	Viral vector	None	New	5 days after 1 <sup>st</sup> dose
14	Female, 46	Korea	Viral vector	None	New	1 day after 1 <sup>st</sup> dose
14	Female, 73	Korea	Viral vector	None	New	14 days after 2 <sup>nd</sup> dose
14	Male, 34	Korea	Viral vector	None	New	14 days after dose
15	Male, 32	Italy	Viral vector	None	New	10 days after 2 <sup>nd</sup> dose
15	Male, 35	Italy	Viral vector	None	New	5 days after 1 <sup>st</sup> dose
16	Female, 34	Belgium	mRNA	GD in remission	Relapse	10 days from 1 <sup>st</sup> dose; symptoms worsened after 2 <sup>nd</sup> dose
9	Female, 71	Austria	mRNA	GD in remission	Relapse	Approximately 1 month from 2 <sup>nd</sup> dose
17	Female, 30	Thailand	Viral vector	GD in remission	Worsening Graves' disease	4 days after booster dose
14	Male, 39	Korea	Viral vector	Not reported	Subacute thyroiditis & Graves'	14 days after dose

Abbreviations: GD – Graves’ disease; TFT – thyroid function test; FT4 – free thyroxine (pmol) (all values converted to pmol/L); TSH – thyroid stimulating hormone (mIU/L); TRAb – TSH receptor antibody (IU/L or IU/ml); TSI – thyroid stimulating immunoglobulin (% or IU/L)

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